II. REMARKS

Preliminary Remarks

Claims 15, 16, 18, 19, 21-24, 26-34 and 36 are canceled, and new claims 38-128 are submitted in their place. Reconsideration and allowance of the present application based on the following remarks are respectfully requested.

New claims 38-128 are directed to the disclosed methodology for obtaining production of a fertilizable oocyte within a program of assisted reproduction technique (ART) comprising administering a luteinizing hormone releasing hormone (LHRH) antagonist in a novel and non-obvious regimen to prevent a premature LH surge, so that fertilizable oocyte can be obtained.

New claims 38-82 are directed to a method for obtaining production of a fertilizable oocyte within a program of controlled ovarian stimulation for assisted reproduction techniques (COS/ART) comprising (a) administering an exogenous gonadotropin to induce follicle growth, and (b) administering a luteinizing hormone releasing hormone (LHRH) antagonist to prevent a premature LH surge, wherein the LHRH antagonist is administered in a single or dual dosage regimen of from 1 to 10 mg per dose; whereby follicular growth occurs in the absence of a LH surge and a fertilizable oocyte is produced. New claims 38-82 are directed to the subject matter of canceled claims 15, 16, 18, 19, 21-24, 26-34 and 36. Support for new claims 38-82 can be found in the specification, for example, on page 5, lines 14-19; page 6, line 3; Table 1, line 3; page 10, lines 13, 15, and 17-19 and originally filed claims 1-4 and 6-14.

Claims 43-49, 55-60, 66-71, and 77-82 are directed to a method for obtaining the production of a fertilizable oocyte comprising administering a LHRH antagonist such as Cetrorelix in either a single or dual dose of 1 to 10 mg, starting cycle day 1 to 10, whereby ovulation occurs between day 9 and 20 of the menstruation cycle. Support for these claims can be found in the specification, for example, on page 5, lines 14-19; and in originally filed claims 7 and 10.

New claims 83-114 are directed to a method for obtaining the production of a fertilizable oocyte within a program of COS/ART comprising (a) administering an exogenous

gonadotropin to induce follicle growth, and (b) administering a LHRH antagonist to prevent a premature LH surge, wherein the LHRH antagonist is administered in a dosage regimen of daily doses of 0.25 mg/day for multiple days, so that follicular growth occurs in the absence of a LH surge and a fertilizable oocyte is produced. Support for new claims 83-114 can be found in the specification, for example, on page 5, line 20, to page 6, line 9, in Table II, and in originally filed claims 1-5 and 10-14.

New claims 85-90, 93-98, 101-106, and 109-114 are directed to a method for obtaining the production of a fertilizable oocyte comprising administering a LHRH antagonist such as Cetrorelix starting cycle day 1 to 10, whereby ovulation occurs between day 9 and 20 of the menstruation cycle. Support for these claims can be found in the specification, for example, on page 5, lines 20-24; and in originally filed claim 10.

New claims 115-128 are directed to a method for obtaining the production of a fertilizable oocyte within a program of assisted reproduction techniques comprising: (a) allowing normal follicular growth and development to proceed in the absence of stimulation by an exogenous gonadotropin; and (b) administering a LHRH antagonist in a dosage regimen that prevents a premature LH surge, with the result that follicular growth and development proceeds in the absence of a LH surge and a fertilizable oocyte is produced. Support for new claims 115-128 can be found in the specification, for example, on page 4, lines 13-27, in Table II, and in originally filed claims 1-4 and 10-14.

The applicants do not intend by these or any amendments to abandon subject matter of the claims as originally filed or later presented, and reserve the right to pursue such subject matter in continuing applications.

Patentability Remarks

Rejection under 35 U.S.C. § 103(a)

Claims 15, 16, 18, 19, 21-24, 26-34, and 37 were rejected as being obvious in view of Diedrich *et al.* (Human Reprod. 9(5):788-791, 1994, hereafter "Diedrich") in view of Felberbaum *et al.* (Eur. J. Obstet. and Gynecol., 61(2):151-155, 1995, hereafter "Felberbaum '95"), for the reasons of record.

Summary of the grounds for rejection

In the initial statement of the obviousness rejection, original claims 1-14 were rejected under 35 U.S.C. § 103(a) as being obvious in view of Diedrich, further in view of Felberbaum '95, in the official action dated December 1, 1997. The official action stated:

> *"Diedrich et al. disclose a method of inducing ovarian stimulation in tubal sterile patients by administering a combination of exogenous gonadotrophins (HCG) and the LHRH antagonist Cetrorelix to said patients. Cetrorelix was administered at a dosage 3 mg daily starting on day 7 of the menstrual cycle. Diedrich also disclose that GnRH agonists given in combination with exogenous gonadotrophins also results in more effective stimulation. (citation omitted).*
>
> *Diedrich does not specifically teach treating infertility, yet the Examiner refers to Felberbaum et al., which teaches treating women with tubal infertility with a combination of exogenous gonadotropins (HMG) and Cetrorelix, wherein the Cetrorelix is administered subcutaneously at 3 mg or 1 mg daily starting on day 7 of the menstrual cycle. (the abstract is cited). It would have been obvious to one of ordinary skill in the art to use the method taught by Diedrich to treat infertility because Felberbaum raises expectation of success by disclosing that ovarian stimulation is induced and further because Felberbaum, in addition to Diedrich, teaches that the disclosed treatment would be effective in the treatment Polycystic Ovarian Disease [sic]. Furthermore, both Diedrich and Felberbaum disclose administration of the same gonadotropin/Cetrorelix combination to a patient using the same method steps and dosages set forth in Applicant's claims. Accordingly, treatment of fertility disorders would have been obvious.*
>
> *With respect to using LH, LHRH, or a LHRH agonist to inducing ovulation instead of HCG (taught by art), such a modification would have been obvious to one of ordinary skill in the art because it is known that the overall effect of LH and its agonists are [sic] to induce ovulation.*
>
> *Finally, concerning claim 5, which recites administration of Cetrorelix in an amount in the range of 0.1 to 0.5 mg, optimization of dosage amounts is well within the capability of the skilled artisan."*

The official action dated October 24, 2000, further stated that, with respect to using a dose regimen of 0.25 mg Cetrorelix/day:

"since Diedrich and Felberbaum have established that the efficacy of Cetrorelix is dependent upon its concentration, it would have been obvious to one of ordinary skill in the art to further modify the method of Diedrich and Felberbaum such that Cetrorelix is present in a dose regimen that is effective to optimize its effect on ovarian stimulation."

The official actions dated June 22, 1998; December 10, 1998; March 3, 1999; August 18, 1999; February 1, 2000; July 11, 2000; October 24, 2000; August 27, 2002; and November 3, 2003, continued to reject all pending claims under 35 U.S.C. § 103(a) as being obvious in view of Diedrich, further in view of Felberbaum, reiterating the grounds for rejection that were applied against the originally filed claims in the official action dated December 1, 1997.

Response to the rejection

Both Diedrich and Felberbaum describe methods for stimulating superovulation in tubal sterile patients comprising (a) administering exogenous gonadotropins (LH, FSH, and HMG) starting on day 2 of the menstrual cycle to stimulate follicle growth, (b) administering a daily dose of 1-3 mg of the LHRH antagonist Cetrorelix starting from day 7 and continuing, on average, for about 5 days, until about day 12, when ovulation was induced by the administration of exogenous HCG (see p. 789 of Diedrich; and p. 153 of Felberbaum).

With regard to the invention of claims 38-82, neither Diedrich nor Felberbaum described or suggested a method for obtaining the production of a fertilizable oocyte within a program of COS/ART wherein the LHRH antagonist is administered in a single or dual dosage regimen of from 1 to 10 mg per dose. The cited references only describe methods wherein daily doses of the LHRH antagonist are administered over a period averaging about five days. At the time the priority application was filed, persons of ordinary skill in the art recognized that ovulation leading to production of a fertilizable oocyte is a complex physiological phenomenon that is highly sensitive to changes in the absolute and relative concentrations of the gonadotropins LH and FSH, the steroids estrogen and progesterone, and gonadotropin releasing hormone, which regulates the secretion of LH and FSH. At the time the priority application was filed, **it would have been impossible for one of ordinary skill in the art to predict that a COS/ART method with a regimen of a single administration**

or dual administrations of an LHRH antagonist would successfully prevent premature LH surges and permit the recovery of fertilizable oocytes.

With regard to the method of claims 83-114, neither Diedrich nor Felberbaum described or suggested a method for obtaining the production of a fertilizable oocyte within a program of COS/ART wherein the LHRH antagonist is administered as a daily dose of as little as 0.25 mg. In fact, as noted in an earlier response, Felberbaum expressly states that the role of luteal support in oocyte development was poorly understood, and that it was unknown whether a COS/ART procedure employing daily doses of less than 0.5 mg of Cetrorelix would be successful (p. 154, last paragraph). As with the method using single or dual doses, **one of ordinary skill in the art could not have predicted that a COS/ART method with a regimen of daily doses of as little as 0.25 mg of a LHRH antagonist would successfully prevent premature LH surges and provide fertilizable oocytes.**

With regard to the method of claims 115-128, neither Diedrich nor Felberbaum described or suggested a method for obtaining the production of a fertilizable oocyte within a program of assisted reproduction techniques comprising allowing normal follicular growth and development to proceed in the absence of stimulation by an exogenous gonadotropin, administering a LHRH antagonist in a dosage regimen that prevents a premature LH surge, and either allowing ovulation to occur normally, or inducing ovulation by administering a hormone or hormone agonist selected from the group consisting of native LH, recombinant LH, an LHRH agonist, and HCG. The method of claims 115-128 is fundamentally different from that described by Diedrich and Felberbaum. There is simply no suggestion in either Diedrich and Felberbaum to modify the methods disclosed in the prior art to give the claimed method wherein normal follicular growth and development proceed in the absence of stimulation by an exogenous gonadotropin.

A *prima facie* obviousness requires: (1) some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; (2) the teaching or suggestion of all the claim limitations of the applicant's invention in the combined prior art references; and (3) a reasonable expectation of success. M.P.E.P. § 2143. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found

in the prior art, not in applicant's disclosure." *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). Moreover, the prior art must provide some teaching, suggestion or motivation to make the specific combination that was made by the applicant." *In re Dance*, 160 F.3d 1339, 1343, 48 USPQ2d 1635, 1637 (Fed. Cir. 1998) (emphasis added) (citing *In re Raynes*, 7 F.3d 1037, 1039, 28 USPQ2d 1630, 1631 (Fed. Cir. 1993); *In re Oetiker*, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1445 (Fed. Cir. 1992).

The Diedrich and Felberbaum references did not disclose or suggest the methods to which new claims 38-128 are directed, nor would they have provided one of skill in the art with a reasonable expectation of their success. Accordingly, the applicants submit that the claimed invention was not obvious in view of the prior art references, and respectfully request that the rejection of claims based on 35 U.S.C. § 103(a) be withdrawn

Provisional rejection for obviousness-type double-patenting:

The pending claims were rejected for obviousness-type double-patenting with respect to claims 22-25, 30, 31, 33, 36-39, and 41-48 of co-pending Application No. 09/053,132, which has been abandoned in favor of continuation Application No. 10/661,780, filed September 15, 2003. To the extent that the amended claims remain subject to the provisional obviousness-type double-patenting rejection, the applicants will file a terminal disclaimer to overcome the rejection upon indication that claims at issue are allowable.

III. CONCLUSION

All objections and rejections having been addressed, it is respectfully submitted that the present application is in condition for allowance and a Notice to that effect is earnestly solicited. If any points remain in issue, which the examiner feels may be best resolved through a personal or telephone interview, he is kindly requested to contact the undersigned attorney at the telephone number listed below.

Respectfully submitted,

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